It should be noted that the characteristic feature of complexes XIII-XIX, obtained from VI, is the practically complete coincidence of the MIC and MBC values, which indicates that they have a bactericidal type of action. To confirm this supposition, we studied the bactericidal properties of complex XVII having the highest activity of the synthesized compounds (the MIC and MBC vary from 1.25 to 75 μg/ml). The experiment showed that the microorganisms used as test cultures have varied sensitivity towards XVII. The most pronounced activity was shown by this complex with respect to B. anthracis: even after 1 h, in all concentrations XVII showed an absolute bactericidal effect. With respect to Escherichia coli, Staphylococcus and Proteus, compound XVII has a bactericidal effect after 1 h in a concentration of 500 μg and above. At a more prolonged exposure (3 h and more), the bactericidal effect is manifested with respect to all strains of microorganisms studied, starting from 100 μg/ml and above.

In view of the short time of exposure (1 h) and the low concentration used, complex XVII may have promise as a disinfectant or antiseptic.

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SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF 2-SUBSTITUTED 5-ARYL-2,3-DIHYDRO-3-FURANONES AND 1,6-DIARYL-3,4-DIHYDROXY-2,4-HEXADIEN-1,6-DIONES*

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Derivatives of 3-furanones are known to have a wide spectrum of biological activity [3, 14, 22]. Representatives include compounds possessing anticoagulant [19], antiatherosclerotic, hypotensive [5], fungicide [18], herbicidal [9], and bactericidal [14, 17] as well as other forms of activity [3, 14, 22]. Some natural materials possessing antitumor properties such as yatrophone [21, 22], the eremantolides A, B, and C [16, 22], geiparvarin [20, 22], and bullatenon [22, 23] also contain the 3-furanone fragment. In this connection a search for new biologically-active compounds as potential drugs among the derivatives of 3-furanones had good prospects.

In a search for compounds possessing antimicrobial activity among the 2-substituted 5-aryl-2,3-dihydro-3-furanones, we prepared 5-aryl-2-acylmethylene-2,3-dihydro-3-furanones [I-XXXVI] by reaction of 5-aryl-2,3-dihydro-2,3-furandiones with acylmethylenetriphenylphosphoranes [1, 2, 6].

The physicochemical and spectral characteristics of I, II, IV-VII, and XVIII-XXI were presented in [1, 2], of IX, X, XV, and XXV-XXVII in [1], and of XI-XIII, XXII and XXIII

*Communication V in the series "Chemistry of 2-Methylene-2,3-dihydro-3-furanones". For communication IV, see [7].

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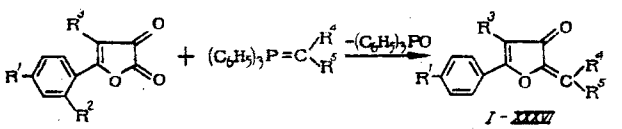
TABLE 1. Physicochemical Characteristics of 2-Substituted 5-Aryl-2,3-dihydro-3-furanones and 1,6-Diaryl-3,4-dihydroxy-2,4-hexadien-1,6-diones

Compound	Yield, %	mp, °C	Empirical formula
III	83	144—145	$C_{15}H_{14}O_4$
VIII	81	185—186	$C_{13}H_9FO_4$
XIV	36	98—99	$C_{15}H_{14}O_4$
XVI	83	117—118	$C_{14}H_{11}BrO_4$
XVII	78	206—207	$C_{13}H_8ClIO_4$
XXIV	76	140—141	$C_{14}H_{10}BrClO_4$
XXVIII	68	147—148	$C_{12}H_6BrNO_6$
XXIX	66	155—156	$C_{13}H_8ClNO_2$
XXX	82	167—168	$C_{18}H_{11}BrO_3$
XXXI	71	160—161	$C_{19}H_{13}BrO_3$
XXXIII	45	145—146	$C_{20}H_{15}BrO_3$
XXXV	47	212—213	$C_{18}H_{11}NO_5$
XXXVI	33	174—175	$C_{19}H_{13}NO_6$
XXXVII	92*	103—104	$C_{13}H_{10}Br_2O_4$
XXXIX	69*	67—68	$C_{14}H_{11}Br_3O_5$
XLII	65*	118—119	$C_{13}H_8Cl_4O_4$
XLIV	93	194—195 (Dec.)	$C_{18}H_{13}BrO_4$
XLV	88	230—231 (Dec.)	$C_{19}H_{15}BrO_4$
XLVI	92**	231—232 (Dec.)***	$C_{18}H_{12}Cl_2O_4$
XLVII	85	235—236	$C_{18}H_{13}NO_6$

*Yield by Method A.
**Yield = 80% by the method of [15].
***mp = 229°C [13, 15].

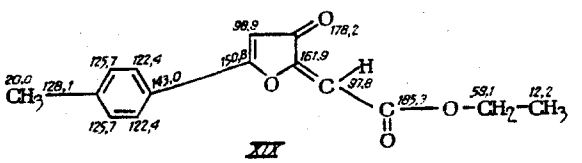
in [6]. The structurally-similar 2-(p-halobenzoylmethylene)-5-p-halophenyl)-2,3-dihydro-3-furanones XXXII and XXXIV were obtained earlier by heterocyclization of 1,6-bis-(p-halophenyl)-3,4-dihydroxy-2,4-hexadien-1,6-diones (tetraketones) by the action of acetic anhydride in the presence of pyridine [15]. The chacteristics of the new methylene furanones are presented in Table 1. The structures of the compounds obtained were verified by IR, ^1H NMR, and ^{13}C NMR spectroscopy, mass spectrometry, and elemental analysis.



I-XXXVII

R^1=H (I, IX, XV, XVIII, XXV, XXVIII, XXX, XXXV), CH_3 (II, III, XII, XIV, XVI, XIX, XXII, XXVI, XXIX, XXXI, XXXIII), CH_3O (IV, X, XIII, XX, XXXVI), C_2H_5O (V, XXIII), Br (VI, XI, XXI, XXXII), Cl (VII, XVII, XXIV, XXVII, XXXIV), F (VIII); R^2=H (I, II, IV—XXXII, XXXIV—XXXVI), CH_3 (III, XXXIII), R^3=H (I—VIII, XIV—XXI, XXIV—XXVII, XXX—XXXVI), CH_3 (IX, X), Br (XI, XXVIII), Cl (XII, XIII, XXII, XXIII, XXIX); R^4=H (I—XIII, XVIII—XXIII, XXV—XXXVI), CH_3 (XIV), Br (XV, XVI, XXIV), I (XVII), R^5=$COOCH_3$ (I—XVII), $COOC_2H_5$ (XVIII—XXIV), CN (XXV—XXIX), COC_6H_4Br-p (XXX—XXXIII), COC_6H_4Cl-p (XXXIV), $COC_6H_4NO_2$-p (XXXV, XXXVI).

The ^{13}C NMR spectra of the methylene furanone XIX showed signals for the nuclear carbon atoms with the following values of chemical shift (ppm) which indicates the structure of the compounds obtained:

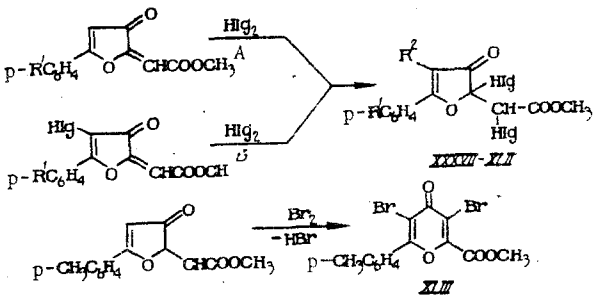


XIX

TABLE 2. Physicochemical and Spectral Characteristics of 4-pyranones XLIII and 2-Hydroxy-2,3-dihydro-3-furanones LI-LV

Compound	Yield %	mp., °C	Empirical formula	IR spectrum, ν, cm^{-1}, crystals	^1H NMR spectrum, δ, ppm, $CDCl_3$
XLIII	47	175—176	$C_{14}H_{10}Br_2O_4$	1725($COOCH_3$), 1715(C^4=O), 1580—1595(C=C)	2,43(3H, s, CH_3); 3,97(3H, s, CH_3O); 7,18, 7,65(4H, dd, C_6H_4)
LI	38	114—115	$C_{13}H_{12}O_5$	3080—3120(OH), 1712 ($COOCH_3$), 1667(C^3=O), 1560, 1588(C=C)	2,79(2H, dd, CH_2); 3,67(3H, s CH_3O); 5,88(1H, s, CH); 6,81(1H, s, OH); 7,15—7,90(5H, m, C_6H_5)
LII	43	129—130	$C_{14}H_{14}O_5$	3110—3140(OH), 1718 ($COOCH_3$), 1675(C^3=O), 1560, 1585(C=C)	2,45(3H, s, CH_3); 2,85(2H, dd CH_2); 3,83(3H, s, CH_3); 5,98(1H, s CH); 6,95 (1H, s OH); 7,34, 7,83(4H, dd, C_6H_4)
LIII	65	120—121	$C_{14}H_{14}O_6$	3110—3140(OH), 1713 ($COOCH_3$), 1672(C^3=O), 1570, 1595(C=C)	2,87(2H, dd, CH_2); 3,75(3H, s, CH_3O); 3,90(3H, s, CH_3O); 5,94(1H, s, CH); 6,89 (1H, s, OH); 7,17, 7,92(4H, dd, C_6H_4)
LIV	48	145—146	$C_{13}H_{11}BrO_5$	3110—3140(OH), 1707 ($COOCH_3$), 1675(C^3=O), 1565, 1585(C=C)	2,88(2H, dd CH_2); 3,81(3H, s CH_3O); 6,03(1H, s, CH); 6,95(1H, s, OH); 7,68 (4H, s, C_6H_4)
LV	73	140—141	$C_{13}H_{11}ClO_5$	3120—3150(OH), 1711 ($COOCH_3$), 1683(C^3=O), 1570, 1592(C=C)	2,78(2H, dd, CH_2); 3,71 (3H, s CH_3O); 5,89(1H, s, CH); 6,77(1H, s, OH); 7,22 7,51(4H, dd, C_6H_4)

The reaction of 5-aryl-2-methoxycarbonylmethylene-2,3-dihydro-3-furanone (Method A) or its 4-halo derivative (Method B) with bromine or chlorine in tetrachloromethane at room temperature lead to the formation of 5-aryl-2-halo-2-methoxycarbonylhalomethyl-2,3-dihydro-3-furanones (XXXVII-XLII). The bromination of 2-methoxycarbonylmethylene-5-(p-tolyl)-2,3-dihydro-3-furanone under analogous conditions gave 3,5-dibromo-2-methoxycarbonyl-6-(p-tolyl)-4H-4-pyranone (XLIII) in a yield of 47%.



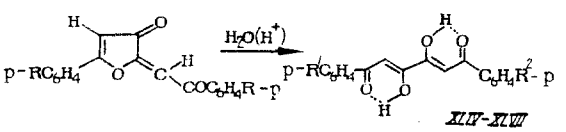
XXXVII-XLII

XLIII

R^1=H (XXXVII, XL), CH_3 (XXXVIII, XLI), CH_3O (XXXIX), Cl (XLII); R^2=H (XXXVII), Br (XXXVIII, XXXIX), Cl (XL—XLII); Hlg=Br (XXXVII—XXXIX), Cl (XL—XLII)

The physicochemical and spectral characteristics of compounds XXXVIII, XL, and XLI are given in [6], and the constants of all the remaining newly-prepared compounds are given in Tables 1 and 2.

The 2-(p-halobenzoylmethylene)-5-(p-halophenyl)-2,3-dihydro-3-furanones are known to add water upon stirring with 70% acetic acid in the presence of pyridine, leading to the formation of a decyclization product: 1,6-bis-(p-halophenyl)-3,4-dihydroxy-2,4-hexadien-1,6-dione [15]. Conducting the hydration of 5-aryl-2-aroylmethylene-2,3-dihydro-3-furanones in acetone in the presence of hydrochloric acid allows the preparation in high yield of the 1,6-diaryl-3,4-dihydroxy-2,4-hexadien-1,6-diones (XLIV-XLVII).

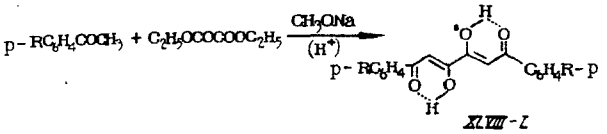


XLIV-XLVII

R^1=H (XLIV, XLVII), CH_3 (XLV), Cl (XLVI); R^2=Br (XLIV, XLV), Cl (XLVI), NO_2 (XLVII).

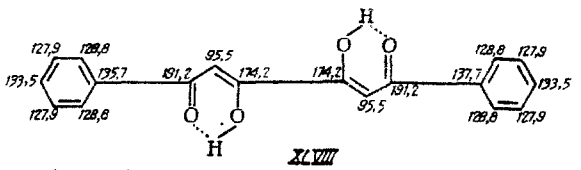
Compound XLVI was identical to the known 3,4-dihydroxy-1,6-bis-(p-chlorophenyl-2,4-hexadien-1,6-dione [13, 15]. Upon cyclodehydration of compound XLVI with trifluoroacetic anhydride in the presence of pyridine in chloroform the methylene furanone XXXIV was obtained

in a yield of 76%. Characteristics of the newly synthesized compounds are presented in Table 2. For comparison of the antimicrobial activity in this series we also obtained the known 1,6-diaryl-3,4-dihydroxy-2,4-hexadien-1,6-diones (XLVI and XLVIII-L) by the method of Claisen [12, 13] involving cyclocondensation of diethyl oxalate with a 2-fold excess of p-substituted acetophenone in the presence of sodium methylate in ether.



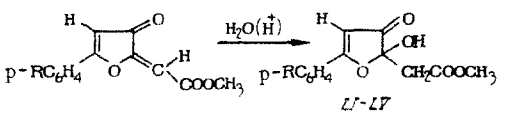
R=H (XLVIII), CH_3 (XLIX), C_2H_5O (L)

Compounds XLIV-L earlier given the name 1,6-diaryl-1,3,4,6-tetraketone [12,13], existed in the dienol form, stabilized by intramolecular hydrogen bonding in the form of the bis(H-chelate) [15], which was proven by ^{13}C NMR spectroscopy data (for example compound XLVIII) which corresponded well with the spectral data of the structurally-similar methyl ester of benzoylpyrotartaric acid [4]:



Upon carrying out the hydration of 5-aryl-2-methoxycarbonylmethylene-2,3-dihydro-3-furanone under analogous conditions, we unexpectedly isolated the cyclic products of the addition of water; 5-aryl-2-hydroxy-2-methoxycarbonylmethyl-2,3-dihydro-3-furanones (LI-LV), (see Table 2).

The presence in the ^1H NMR spectra of compounds LI-LV of two doublets of the two interacting geminal protons of the CH_2 group at 2.78-2.88 ppm, and also the lower field signals of the hydroxyl group protons at 6.77-6.95 ppm (Table 2) confirms that the structure of compounds obtained is not that of the methyl esters of 6-aryl-4-hydroxy-3,6-dioxo-4-hexenoic acid.



R=H (LI), CH_3 (LII), CH_3O (LIII), Br (LIV), Cl (LV)

EXPERIMENTAL (CHEMISTRY)

IR spectra of the compounds were recorded on an UR-20 spectrometer as paste in Vaseline oil. The ^1H NMR spectra were obtained with an RYA-2310 60 MHz instrument in DMSO-d_6 or $CdCl_3$, using hexamethyl disilane as internal standard. ^{13}C NMR spectra were determined with a Bruker HX-90 (90 MHz) spectrometer with TMS as internal standard. The mass spectral data were recorded with a Varian MAT-311 apparatus using direct sample injection, an emission current of 1000 mA, an electron ionization energy of 70 eV, and a vaporizer temperature of 120°C. The homogeneity of the compounds was confirmed by TLC on Silufol UV-254 plates, using benzene–ether (3:2) or benzene–ether–acetone (10:9:1) as eluents. Visualization was by means of iodine vapor or UV light.

The characteristics of the synthesized compounds are presented in Tables 1 and 2. Elemental analysis agreed with the calculated values.

5-Aryl-2-acetylmethylene-2,3-dihydro-3-furanones (III, VIII, XIV, XVI, XVII, XXIV, XXVIII-XXXI, XXXIII, XXXV, and XXXVI). To a solution of 5 mmoles of 5-aryl-2,3-dihydro-2,3-furandione in 100-150 ml of benzene was added with stirring 5 mmoles of acylmethylenetriphenylphosphorane and the mixture was heated for 5-15 min. The solvent was evaporated and the residue was recrystallized from ethanol or toluene.

TABLE 3. Antimicrobial Activity of the Synthesized Compounds I-LV

Compound	Laboratory code	Minimal inhibitory concentration (MIC), μg/ml	
		E. coli M17	S. aureus P-209
I	A-2384	Inactive	62,5
II	A-2477	500	500
III	A-2440	Inactive	62,5
IV	A-2467	500	500
V	A-2486	Inactive	Inactive
VI	A-2466	500	1000
VII	A-2479	Inactive	250
VIII	A-2487	Inactive	1000
IX	A-2468	1000	125
X	A-2469	500	1000
XI	A-2480	500	250
XII	A-2057	500	125
XIII	A-2481	500	250
XIV	A-2045	1000	62,5
XV	A-697	125	125
XVI	A-695	125	62,5
XVII	A-2473	500	1000
XVIII	A-2470	Inactive	Inactive
XIX	A-2484	500	500
XX	A-2471	1000	250
XXI	A-2472	500	500
XXII	A-2476	500	125
XXIII	A-2420	1000	500
XXIV	A-696	Inactive	1000
XXV	A-2474	500	250
XXVI	A-2478	Inactive	Inactive
XXVIII	A-1889	Inactive	31,2
XXIX	A-2483	62,5	62,5
XXX	A-2383	125	125
XXXI	A-2423	500	500
XXXII	A-1367	500	62,5
XXXIII	A-2459	500	500
XXXIV	A-2394	Inactive	250
XXXV	A-2393	Inactive	500
XXXVI	A-2465	1000	500
XXXVII	A-2488	500	125
XXXVIII	A-1883	Inactive	62,5
XXXIX	A-2489	Inactive	1000
XL	A-2490	1000	125
XLI	A-2058	500	250
XLII	A-1879	Inactive	15,6
XLIII	A-1884	Inactive	31,2
XLIV	A-2392	1000	500
XLV	A-2452	1000	1000
XLVI	A-2391	Inactive	1000
XLVII	A-2390	Inactive	Inactive
XLVIII	A-2493	Inactive	125
XLIX	A-2491	Inactive	Inactive
L	A-2492	1000	125
LI	A-2042	1000	500
LII	A-2043	1000	1000
LIII	A-2464	1000	500
LIV	A-2454	500	500
LV	A-2245	Inactive	500
Mercury dichloride		1000	1000
Ethacridine lactate		2000	500

2-(p-Chlorobenzoylmethylene)-5-(p-chlorophenyl)-2,3-dihydro-3-furanon XXXIV). To a suspension of 1.82 g (5 mmoles) of 3,4-dihydroxy-1,6-bis-(p-chlorophyl)-2,4-hexadien-1,6-dione (XLVI) in 100 ml of chloroform was added with stirring 0.5 ml of pyridine in 2 ml of trifluoroacetic anhydride. After 3 h, the precipitate was filtered off and recrystallized from toluene to give 1.30 g (76%) of compound XXXIV with mp = 184-185°C (lit. mp = 188°C [5]).

5-Aryl-2-halo-2-methoxycarbonylhalomethyl-2,3-dihydro-3-furanones (XXXVII, XXXIX, XLII). To a suspension of 5 mmoles of 5-aryl-2-methoxycarbonylmethylene-2,3-dihydro-3-furanone (Method A) or 5-aryl-4-halo-2-methoxycarbonylmethylene-2,3-dihydro-3-furanone (Method B) in 100 ml of tetrachloromethane at room temperature was added with stirring 6 mmoles of bromine (synthesis of compounds XXXVII and XXXIX) or a stream of chlorine was passed (synthesis of compound XLII) until solution of the solid. The solvent was evaporated under vacuum, the residue was triturated with ether, and recrystallized from ethanol.

3,5-Dibromo-2-methoxycarbonyl-6-(p-tolyl)-4H-4-pyranone XLIII) was obtained analogously to compounds XXXVII and XXXIX (Method A). The material was purified by crystallization from ethanol. Mass spectrum , m/z* (% of max peak); 400(16) M^+, 370(6) $M-CH_3OH^+$, 341(4) $M-CH_3OCO^+$, 321 $M-Br^+$, 194(27) $p\text{-}CH_3C_6H_4C\equiv CBr^+$, 143(100) $p\text{-}CH_3C_6H_4C\equiv C-C\equiv O^+$, 119(54) $p\text{-}CH_3C_6H_4C\equiv O^+$, 115(69) $p\text{-}CH_3C_6H_4C\equiv C^+$, 91(39) $p\text{-}CH_3C_6H_4^+$, 69(60) $O\equiv C-CH=C=O^+$.

1,6-Diaryl-3,4-dihydro-2,4-hexadien-1,6-diones (XLIV-XLVII). To a solution of 5 mmoles of 5-aryl-2-aroylmethylen-2,3-dihydro-3-furanone in 100-150 ml of acetone at 40-50°C was added with stirring 2 ml of hydrochloric acid. After 1 h the precipitate was filtered off and recrystallized from chloroform or toluene.

5-Aryl-2-hydroxy-2-methoxycarbonylmethyl-2,3-dihydro-3-furanones (LI-LV) were obtained analogously to compounds XLIV-XLVII. The materials were purified by recrystallization from ethanol or acetonitrile.

EXPERIMENTAL (BIOLOGY)

All of the synthesized compounds were tested for antimicrobial activity.

The acute toxicity LD_{50} of these compounds was obtained by the method of G. N. Pershin [10]. The compounds were introduced intraperitoneally into white mice weighing 20-24 g in the form of a suspension in 2% starch paste. The antimicrobial activity was obtained by comparison with standard samples of Escherichia coli M_{17} and Staphylococcus aureus P-209 carried out by the standard 2-fold serial dilution method in liquid nutrient medium (meat peptone bouillon) [10]. The bacterial load for the experiments were evaluated 18-20 h after introduction of the control and experimental sample into a thermostat at 36-37°C. The presence or absence of bacterial growth as a result of the bacteriostatic action of the compounds was recorded. The effect of the dose was used to determine the minimal inhibitory concentration (MIC) for the compound; i.e., the maximum dilution resulting in complete suppression of growth of the test microbe. The antimicrobial activity of the prepared compounds (Table 3) was compared with the activities of mercury dichloride ('corrosive sublimate') [8, 11] and ethacridine lactate, an antimicrobial preparation widely used in medicine [8].

The acute toxicity of the experimental materials exceeded 600 mg/kg, except for compound XVI, the LD_{50} of which was 17.0 (12.6-22.9) mg/kg. Thus, practically all of the studied compounds were of far lower toxicity than the comparison preparation, mercury dichloride LD_{50} = 3.9 mg/kg) and ethacridine lactate (70.0 mg/kg). The results of the studies carried out on the antimicrobial activity of these compounds showed antibacterial activity over a wide range of MIC: from 1000 to 15.6 μg/ml; some of them were inactive (Table 3). The highest activity with respect to E. coli was shown by compound XXIX (MIC = 62.5 μg/ml), and with respect to S. aureus, by compound XLII (15.6 μg/ml). A significant dependence of the acute toxicity and bacteriostatic activity on the chemical structure of these materials could not be detected.

Thus, antimicrobial activity with insignificant toxicity has been found among a large number of 2-substituted 5-aryl-2,3-dihydro-3-furanones and related compounds.

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SYNTHESIS, ANTIBACTERIAL AND ANTIFUNGAL PROPERTIES OF 1-THIOCYANATO-1-CHLORO- AND 1-THIOCYANATO-1,1-DICHLORO-2-ARYLETHANES

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The antimicrobial properties of 1-thiocyanato-1-alkoxycarbonyl-2-arylethanes have been studied [2, 3]. Structure–activity studies to correlate their physiological activity with their structures have been performed. Alkylaromatic thiocyanates containing halogen substituents within the alkyl chain are especially interesting. These compounds have been synthesized by anion arylation using easily accessible alkenes such as vinyl chloride and vinylidene chloride as the starting materials.

We have now found that aryldiazonium tetrafluoroborates react vigorously with vinyl chloride and vinylidene chloride in acetone or acetone–water (4:1) solutions in the presence of potassium, sodium, or ammonium thiocyanate. The reactions proceed with the elimination of nitrogen from the diazonium group and addition of the aryl and thiocyanato groups to the double bond of the monounsaturated alkene to give 1-thiocyanato-1-chloro- and 1-thiocyanato-1,1-dichloro-2-arylethanes:

$$R^1C_6H_4N_2^+BF_4^- + CH_2{=}CR^2Cl + MSCN \rightarrow R^1C_6H_4CH_2\underset{\underset{SC{\equiv}N}{|}}{C}R^2Cl + N_2 + MBF_4$$

I–VI

R = H (I, IV), p-CH_3 (II, V), p-CH_3O (III, VI); R = H (I–III), Cl (IV–VII); M = Na, K, NH_4

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